

## Correlation between the stress scale with cortisol levels in leprosy patients



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### ABSTRACT

**Introduction:** Leprosy is an infectious disease caused by *Mycobacterium leprae* (*M. leprae*) that causes a complex problem. Stress can trigger several physiological responses, including the endocrine, nervous, and immune systems. In leprosy patients, stimulation in the form of infection and cytokine secretion lasts a long time, causing adrenal exhaustion, resulting in decreased serum cortisol production. This study aims to determine the correlation between the stress scale and cortisol levels in leprosy patients.

**Methods:** This was a cross-sectional analytic correlation study with a consecutive sampling method. The research subjects were obtained from the Dermatology and Venereology Polyclinic of Universitas Sumatera Utara Hospital and the Dermatology and Venereology Polyclinic of Dr. Pirngadi Hospital Medan from March until November 2020. The research variables consisted of a stress scale and cortisol levels. Data analysis using the Spearman test. P-value <0.05 was significant. The study was conducted after approval from the Ethics Committee Faculty of Medicine, Universitas Sumatra Utara.

**Result:** A total of 35 patients enrolled in the study, the majority had characteristics of the male gender, multibacillary type of leprosy, duration of leprosy in the group > 12 months, with a median age of 36 (19 - 79) years. The mean stress scale was  $15.17 \pm 6.3$ , with the mild stress scale was the most common. The median cortisol levels were 9.5 (4 - 20,8) g/dl, which was still in the low category. The lowest median cortisol levels were found in the multibacillary type of leprosy, duration of leprosy in the group > 12 months, and severe stress scale. There was a significant moderate negative correlation between the stress scale and cortisol levels in leprosy patients ( $p = 0.017$ ;  $r = -0.402$ ).

**Conclusion:** The heavier the stress scale, the lower the cortisol levels in leprosy patients.

**Keywords:** leprosy, stress, cortisol.

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### INTRODUCTION

Leprosy is a contagious disease caused by *Mycobacterium leprae* (*M. leprae*) that causes very complex problems.<sup>1,2</sup> Leprosy develops slowly and can cause dysfunction and severe nerve damage, which can lead to disability.<sup>2,3</sup> The prevalence of leprosy globally in 2017 was 0.3 / 10,000 population, and this disease affects all ages, men, and women, and most of them are in young adults who are of productive age.<sup>4,5</sup>

Leprosy patients tend to live alone and reduce social activities with their surrounding environment. They depend on other people, feel pressured and ashamed to seek treatment, experience limitations or inability to work, or receive discrimination to get human rights so that life's necessities cannot be fulfilled.<sup>2,6,7</sup> This situation can lead to frustration and even

suicide attempts. The stigma that is formed can also cause reluctance to seek treatment for fear of being known to the surrounding community.<sup>2</sup>

Stress occurs when the external environment brings pressure, conflict, anxiety, and frustration to the individual.<sup>8</sup> According to research conducted by Hane et al., it is reported that the disability caused by leprosy patients is related to psychological stress ( $p < 0.001$ ;  $r = 0.42$ ). In this study, the correlation between leprosy and stress reaction shows that the heavier the leprosy reaction obtained by leprosy patients, the higher the stress level, which is a risk factor that affects the occurrence of leprosy reactions and contributes 33.43%.<sup>9</sup>

Stress can trigger several physiological responses, including the endocrine, nervous, and immune systems. This physiological stress response involves activation of the hypothalamus-pituitary-

adrenal (HPA) axis and the sympathetic-adrenal-medulla (SAM) axis, both of which interact with immune function. Activation of the HPA axis will induce activation of key stress hormones, including corticotropin-releasing hormone (CRH) in the hypothalamus, adreno-corticotrophic hormone (ACTH) in the anterior pituitary, and cortisol in the adrenal cortex. These hormones, which disrupt the balance of cellular immunity mediated by T helper 1 (Th1), and humoral immunity are mediated by T helper 2 (Th2).<sup>10,11</sup>

Leprosy is a chronic disease with several acute episodes of reactions, so that it can be categorized as a severe disease because of its effects on several organ functions. One of the organs in the body that is affected is the adrenal gland. In an acute state, CRH and ACTH's secretion will increase and stimulate an increase

in adrenal glucocorticoids. In patients with leprosy, stimulation in the form of infection and cytokine secretion lasts a long time, causing adrenal exhaustion. The adrenal cortex is resistant to stimulation and causes a decrease in serum cortisol production.<sup>12,13</sup> Researchers were interested in investigating the correlation between the stress scale with cortisol levels in leprosy patients to see if the heavier the stress scale, the lower the cortisol levels in leprosy patients.

## METHODS

This study was conducted after obtaining approval from the Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara, North Sumatra, Indonesia, with registry number 82/KEP/USU/2020. This study was a cross-sectional analytic correlation study with a consecutive sampling method. The research subjects were obtained from the Dermatology and Venereology Polyclinic of Universitas Sumatera Utara Hospital and the Dermatology and Venereology Polyclinic of Dr. Pirngadi Hospital Medan from March 2020 until November 2020. The inclusion criteria are patients who have been diagnosed with leprosy are  $\geq 18$  years old and agree to follow the research by filling out and signing the research informed consent form. Leprosy patients who received corticosteroid therapy  $>3$  weeks or had stopped corticosteroid therapy for  $<1$  month; who have a history of chronic diseases such as chronic renal failure, stroke, an acquired immunodeficiency syndrome (AIDS), diabetes mellitus, hypertension, hyperlipidemia, depression, anxiety, autoimmune, and cancer; who have a history of steroid-controlled asthma; and with Chusing's syndrome were excluded from this study.

The selected patients were subjected to anamnesis, physical examination, interview for filling out the questionnaire, and blood sampling. The stress scale was determined based on Perceived Stress Scale-10 (PSS-10) questionnaire, where normal (score 0), mild (score 1 – 14), moderate (score 15 – 26), and severe (score  $> 26$ ). The cortisol levels were measured using an enzyme-linked immunosorbent assay (ELISA) method, where normal

**Table 1. Characteristics of research subjects**

Characteristics	Median (min-max) or mean $\pm$ SD	n (35)	Percentage (%)
Age (years)	36 (19-79)		
19 – 39		24	68.6
40 – 60		8	22.9
$\geq 61$		3	8.6
Sex			
Male		22	62.9
Female		13	37.1
Type of leprosy			
Paucibacillary		6	17.1
Multibacillary		29	82.9
Duration of leprosy (months)			
1 - 6		9	25.7
$> 6 - 12$		10	28.6
$> 12$		16	45.7
Stress scale	15.17 $\pm$ 6.3		
Mild		19	54.3
Moderate		14	40
Severe		2	5.7
Cortisol levels (g/dl)	9.5 (4 – 20.8)		

Note: SD = standard of deviation

**Table 2. Characteristics of cortisol levels**

Characteristics	Cortisol levels (g/dl)	
	Median	Minimum - maximum
Type of leprosy		
Paucibacillary	11.25	7.6 – 13.8
Multibacillary	8.1	4 – 20.8
Duration of leprosy (months)		
1 – 6	10.3	5.3 – 13.8
$> 6 - 12$	9.9	4.3 – 20.4
$> 12$	7.95	4 – 20.8
Stress scale		
Mild	10.9	5.2 – 20.8
Moderate	7.7	4.3 – 12.3
Severe	5.55	4 – 7.1

**Table 3. Correlation between the stress scale with cortisol levels**

Stress scale	Cortisol levels

Note: \*significant at  $p < 0.05$  by Spearman correlation test

cortisol serum levels  $> 10$  g/dl.

## Statistical analysis

The collected research data will be analyzed statistically used a computer program. Univariate analysis in this study was conducted to analyze one variable's

characteristics by conducting a descriptive test. Bivariate analysis in this study was conducted to analyze the correlation between research variables to determine the correlation between the stress scale and cortisol levels in leprosy patients by conducting the Spearman correlation

test to determine the significance ( $p$ ) and the correlation ( $r$ ). A  $p$ -value  $<0.05$  was considered statistically significant.

## RESULTS

### Characteristics of research subjects

This study subjects involved 35 leprosy patients who were primarily male (62.9%) with multibacillary leprosy type (82.9%) and duration of leprosy in group  $> 12$  months (45.7%). The study subject's median age was 36 years, with the youngest being 19 years and the oldest being 79 years. The study subject's mean stress scale was  $15.17 \pm 6.3$ , with the most stress scale category being the mild stress scale (54.3%) and the median cortisol levels were 9.5 (4 – 20.8) g/dl which is still in the low category (Table 1). The lowest median cortisol levels were found in multibacillary leprosy (8.1 g/dl), duration of leprosy in group  $> 12$  months (7.95 g dl), and severe stress scale (5.55 g/dl). The characteristics of cortisol levels can be seen in Table 2.

### Correlation between the stress scale with cortisol levels in leprosy patients

A correlation analysis was performed using the Spearman correlation method because the cortisol levels data were not normally distributed. The statistical analysis found a significant moderate negative correlation between the stress scale with cortisol levels in leprosy patients ( $p = 0.017$ ;  $r = -0.402$ ). The results of the correlation can be seen in Table 3.

## DISCUSSION

Leprosy can occur at all ages, but the most common occurrence is in the age range of 20 to 30 years, at a young and productive age because they have a greater risk of being exposed to the source of leprosy transmission.<sup>14,15,16</sup> Theoretically, transmission can occur through prolonged and close contact with people with leprosy.<sup>1</sup> This study had a median age value of 36 (19 – 79) years with the most age range at 19 – 39 years, 24 subjects (68.6%), followed by an age range of 40 – 60 years, eight subjects (22.9%) and three subjects (8.6%) aged  $\geq 61$  years. This study's results are in line with previous research by Sinambela et al., which reported the most age range for leprosy patients was in the

range 19 – 40 years (66.7%).<sup>14</sup> Likewise, Darus et al. reported that leprosy had the highest frequency in the 26 – 35 and 36 – 45 years age group, respectively (32.0%).<sup>17</sup> The reduction of disease transmission was typical in older age. It is also associated with reduced mobility in older age.<sup>16</sup>

Leprosy can affect all sexes, men and women. In this study, it was found that there were more male subjects, 22 subjects (62.9%), compared to females, 13 subjects (37.1%). This result is in line with previous research conducted by Ayudianti et al., which reported that the percentage of men suffering from leprosy (64.28%) was more than women (35.72%).<sup>18</sup> This is also in line with Tami et al., who reported that the percentage of leprosy sufferers in East Java during the last three years was more male than female.<sup>19</sup> This can be caused by social, cultural, and community education factors. In certain cultures, women's access to health services is minimal. The incidence of leprosy is more common in men and is also associated with greater male mobility so that the chance of contact with leprosy patients is increasing.<sup>14</sup>

The classification of leprosy types used in this study is the classification according to World Health Organization (1982). Leprosy patients are divided into two types, the paucibacillary type (PB) and the multibacillary type (MB). In this study, the results showed that most leprosy type in this study were 29 subjects (82.9%) of multibacillary type of leprosy, while six subjects (17.1%) of paucibacillary type of leprosy. This result is in line with previous research conducted at Sanglah General Hospital by Saraswati et al., which reported a higher percentage of multibacillary leprosy (65.7%) than paucibacillary leprosy (34.2%).<sup>20</sup> Sinambela et al. also reported the number of visits of leprosy patients who came for treatment at the Polyclinic of the Department of Dermatology and Venereology at Dr. Pirngadi Hospital and the Polyclinic of the Department of Dermatology and Venereology at USU Hospital in 2018 found more multibacillary type of leprosy than paucibacillary.<sup>14</sup>

In this study, it was found that the majority of duration of leprosy was the group  $>12$  months, 16 subjects (45.7%), followed by the group  $> 6 - 12$  months,

ten subjects (28.6%), and the group 1 – 6 months, nine subjects (25.7%). This study's results are in line with Prawoto's research that reported the most leprosy patients had a duration of suffering from disease  $>12$  months, which affected the emergence of an immune response and leprosy reactions.<sup>21</sup> However, these results were different from research conducted by Ayudianti et al., who reported that the duration of suffering from leprosy patients in their study mainly was at  $>6 - 12$  months (50%), while  $>12$  months was only about 28.57%.<sup>18</sup> The existence of these differences is related to the different patient distributions.

The characteristics of the stress scale were measured using the Perceived Stress Scale-10 (PSS-10) questionnaire. In this study, the mean value of the stress scale for all subjects was  $15.17 \pm 6.3$ , with the most stress scale category being the mild stress scale, 19 subjects (54.3%), followed by a moderate stress scale of 14 subjects (40%) and a heavy stress scale of 2 subjects (5.7%). Research conducted by Prawoto on the incidence of stress in leprosy patients reported that 47.2% of leprosy patients experienced stress. In comparison, 52.8% did not experience stress. A significant relationship between stress, and the occurrence of leprosy reactions ( $p = 0.001$ ), and stress was a risk factor for leprosy reaction (OR = 5.022; 95% CI = 1.991- 12.671).<sup>21</sup> The difference between the results in this study and the previous study may be due to different parameters used in assessing stress. Stress is a triggering factor for leprosy reactions.<sup>2,21,22</sup> Leprosy sufferers who experience emotional stress will tend to need heavy adaptations as well. In a state of stress, the body will experience general disturbances, triggering a leprosy reaction. According to Judith Swarth, stress can result in a decrease in immunity by as much as 50%.<sup>23</sup>

In this study, the median value of cortisol levels for all subjects was 9.5 g/dl which was still low. Based on the type of leprosy, the median value of cortisol levels in the paucibacillary type of leprosy group had a median value of 11.25 g/dl, which was still in the normal category. Meanwhile, the multibacillary type of leprosy group had a median cortisol

level of 8.1 g/dl, which was low. Based on leprosy duration, the median value of cortisol levels in the group of subjects with leprosy duration of 1 – 6 months had a median value of 10.3 g/dl, which was still a normal category. Meanwhile, for subjects in the group of > 6 – 12 months and > 12 months, the median cortisol levels were 9.9 g/dl and 7.95 g/dl, respectively, included in the low category. Based on the stress scale, the median value of cortisol levels in the subject group with a mild stress scale had a median value of 10.9 g/dl, which was still in the normal category. Meanwhile, the subjects with moderate and severe stress scale had median cortisol levels of 7.7 g/dl and 5.55 g/dl, respectively, which were included in the low category.

This study's results are in line with previous research conducted by Ayudianti et al., which reported that the average cortisol levels in leprosy patients were 8.9 g/dl. The average cortisol levels in this study and Ayudianti et al. were both < 10 g/dl, which means it is low.<sup>18</sup> In line with this, Citrashanty et al. also reported a decrease in the average cortisol levels in leprosy patients and the length of time suffering from leprosy. That may be caused by adrenal insufficiency associated with steroid administration or chronic exposure to proinflammatory cytokines.<sup>24</sup> Cortisol is the main glucocorticoid secreted by the human adrenal cortex. In healthy people, free from stress, cortisol is secreted according to diurnal variations under the influence of corticotropin secreted by the pituitary gland.<sup>12</sup> The hypothalamus and pituitary control cortisol secretion. The receptors are found on many cells, so cortisol has various functions in the body in maintaining homeostasis.<sup>25</sup> ACTH secretion increases due to the release of proinflammatory cytokines, then ACTH stimulates the release of adrenal glucocorticoids as feedback. If this cytokine stimulation is chronic, the adrenal cortex will experience fatigue, resulting in decreased serum cortisol. The decrease in serum cortisol appears along with the length of time the patient suffers from leprosy, and the leprosy reaction occurs. Also, corticosteroid therapy can reduce cortisol due to adrenal insufficiency. Secondary adrenal insufficiency can be caused by long-

term administration of corticosteroids or chronic proinflammatory cytokine exposure.<sup>24</sup>

Based on the Spearman correlation test of 35 research samples, it was found that there was a significant correlation between the stress scale and cortisol levels in leprosy patients ( $p = 0.017$ ). The correlation value ( $r$ ) obtained is -0.402, indicating a negative correlation with moderate correlation strength.

Research related to cortisol levels in leprosy patients previously conducted by Ayudianti et al. reported that patients with leprosy history for 1 – 6 months found that the average serum cortisol levels were still within normal limits. Whereas in patients with leprosy history for 7 – 12 months and > 12 months, the average serum cortisol level was lower than normal. The result suggests that chronic exposure to cytokines, especially TNF- $\alpha$  and IL-6 in leprosy, can cause a decrease in serum cortisol levels.<sup>18</sup> In this study, the leprosy duration characteristics were mainly in the > 6 – 12 months and > 12 months group. This result is in line with Ayudianti et al., wherein the exposure to acute conditions when the TNF- $\alpha$  produced is very high can interfere with the secretion of ACTH, causing decreased serum cortisol levels. After the acute period passes, the body then compensates so that the cortisol also increases (negative feedback from the HPA axis).<sup>26</sup>

Stress conditions in the body will result in elevated ACTH, which will activate biosynthesis and release glucocorticoids from the adrenal cortex. These steroids will become important receptors that affect gene expression and general body regulation that require energy and cause metabolic changes in the body as a coping process for stressors.<sup>27</sup> Cortisol also has an essential role in helping the body deal with stress, known as the primary stress hormone. If the stress response is activated too frequently, the body does not always have the opportunity to return cortisol levels to normal ranges. It can cause health problems that result from too high or too low circulating cortisol levels.<sup>28,29</sup>

In addition to psychological stress, cortisol levels can also be affected by several conditions, including infectious diseases, inflammation, malignancies

(tumors of the adrenal gland and pituitary gland), drugs (contraceptive pills, amphetamines, and corticosteroids), and pregnancy.<sup>28,29</sup> Strenuous activity, namely activity or exercise at an intensity above 60% maximum oxygen uptake for 30 minutes, can also affect circulating cortisol levels.<sup>30</sup> Stress can directly trigger cortisol levels through ACTH stimulation from the HPA axis to the adrenal cortex in a pathophysiological concept. In leprosy patients, this condition cannot occur linearly because the intensity of exposure to proinflammatory cytokines from leprosy causes adrenal exhaustion, resulting in low cortisol production.

However, this study is not without limitations. One of the factors that affect the value of cortisol levels is the time of blood sampling. In this study, the time for blood sampling was not the same for each subject, wherein the range of 08.00-11.00 WIB could affect the differences in the results of cortisol levels. Besides, stress can be caused by many factors, not only from the disease being suffered by a person (in this study, leprosy) but for other factors not examined in this study. The number of subjects in this study is still relatively small. Further studies with a more significant number of subjects are highly recommended.

## CONCLUSION

There was a significant moderate negative correlation between the stress scale and cortisol levels in leprosy patients. Further research can analyze other factors that can affect cortisol levels in leprosy patients, such as leprosy reactions, disability in leprosy, and steroid administration. It is necessary to manage stress management in leprosy patients.

## DISCLOSURES

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The authors are responsible for all of the study funding without grants or any external funding source.

### Conflict of Interest

The authors declare no conflict of interest regarding the publication of this article.

### Author Contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting, and approval for publication of this manuscript.

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